ANTIMICROBIAL RESISTANCE

PUBLIC MEETING

PRE-APPROVAL STUDIES AND PATHOGEN LOAD

SUMMARY OF BREAKOUT SESSIONS/COMMENTS/CLOSING

THURSDAY, FEBRUARY 24, 2000

8:30 A.M.

DOUBLETREE INN

1750 Rockville Pike

Rockville, Maryland

Main Meeting Room

I N D E X

PRE-APPROVAL STUDIES IN ANTIMICROBIAL RESISTANCE AND PATHOGEN LOAD

BREAKOUT SUMMARIES/COMMENTS/CLOSING

February 24, 2000

Keynote: "---" indicates an inaudible in the transcript.

MICROBIOLOGICAL SAFETY OF DRUG RESIDUES IN FOOD

(2:00 p.m.)

INTRODUCTION

By: Dr. Sharon Thompson, Chairperson

CHAIRPERSON THOMPSON: We're going to get started, and basically, the purpose of the afternoon session is just to give a summary from each of the sessions in terms of what were the main points that were discussed and what were agreed to.

And once again, this is not really a consensus meeting, but after we do have contributions from each of the moderators of the sessions, there will be an opportunity for public comment.

So if you were in one of the other sessions and one of the points that was brought up in the summary, you'd like to comment on, please feel free to do so after everyone has presented their summary, during the open comment period.

So we'll go ahead and get started and basically everyone is going to try to hold their remarks to no more than fifteen minutes, I think probably less than that from what I understand.

So we'll try to get people out of here early this afternoon on such a beautiful day. So, we're going to go ahead and start with the first session and I think we can tell what species group you're with from your tie.

SUMMARY OF RUMINANTS BREAKOUT SESSION

By: Dr. M. Gatz Riddell, Jr.

DR. RIDDELL: Okay. A couple comments to begin with -- we probably didn't reach consensus. We had considerable discussion. It was a subject of, to borrow a phrase from somebody else, it's hard to get your arms around. I would like to thank my facilitator, Jim Heslin, because this ought to be a big notch on his CV, having worked with a totally untrained moderator.

(Laughter.)

I milk cows; that's all I do, and MICs are something -- they're foreign, so it was -- it was an eye opening experience for me. I'd also like to thank my scribe and like Susan to know that she really wasn't fired but half way through the second session we had, it became apparent to me, the only thing I could do was type and that was my greatest input as far as getting these slides together.

A couple of other things -- I think Tuesday, when I first got up here, I thanked CVM for the invitation; I'll retract that.

(Laughter.)

And you all need to know that Dr. Wages is really from Arkansas so I'm kind of stealing one of his catchy phrases, something I learned from an office man I had, an irascible old fellow from Missouri, years ago, Auburn -- I ain't had this much fun since the hogs ate my brother.

(Laughter.)

So now that I've delayed all I can --

(Laughter.)

We'll begin to talk about a few of the things that were close to consensus when we talk about pre-approval studies for ruminants.

(Slide.)

We felt that there really are, after a day and a half of presentations, no validated studies, or study models existing today, which can predict the rate and extent of resistance development.

Pathogen load studies are highly variable and found no information to consider them predictive relative to public health concerns. We'd like to submit that not all uses and classes of antimicrobials will require the same pre-approval studies as determined via the categorization criteria and the studies to determine such categorization need to be incorporated very early in the developmental process and regulatory review process to determine the fate of new compounds.

(Slide.)

I think it's been stated by many people that resistance is inevitable and that's how we respond to that that is important. Expansion of post-approval monitoring programs are needed to detect resistant trends that may help in the

design of new compounds and strategies to mitigate a problem relative to resistance trends.

(Slide.)

Pretty important, we don't think it's in the arena of pre-approval studies to focus on a status and thresholds. That's for discussions that are entered into as we're creating the post-approval monitoring programs, but the completed pre-approval package would be of utility in establishing certain baselines and certain baseline information.

Pre-approval studies would also be useful in designing the post-approval monitoring process and should provide significant information in that direction.

(Slide.)

Speaking to the categorization of drugs -- our group would like to propose that the sponsor would initially propose a categorization of the drug and that FDA/CVM, concurrent, or modification would be necessary very early in the process to allow things to go forward.

(Slide.)

As we begin to look at answering certain questions and looking at what would be important material to include in pre-approval studies and what would be acceptable when considering concerns of the public health, concerns of industry and concerns of the producer and veterinary groups who are going to be the end users of the products.

Things like the mechanism or mechanisms of action would be significant information as would any data relative to cross-resistance. Mutation frequency data would be useful information to evaluate early on in the process and the compound metabolism such as fecal levels or degree of binding of the drug to fecal matter.

(Slide.)

Pharmacokinetic and pharmacodynamic data would be important and baseline MICs for both target organisms and the NARMS pathogens, utilizing the NCCLS standards. Lastly, a definition, a supported definition of susceptibility for the target organisms for the indications for that compound.

(Slide.)

This information can and should be provided during the product development phase of a discussion with the Center for Veterinary Medicine and this pre-approval information need not be novel studies but may reflect information currently available and validated in the literature.

And, as with most things, further discussion and definition of the studies would be required as the process goes forward.

(Slide.)

When it comes to the topic of sentinel or surrogate organisms -- we had a pretty lively discussion, some proposed models, so there was considerable consideration but it's not

included in our comments.

It was considered but it's not included because the use of sentinel organisms has not been correlated with human food-borne pathogen in the experience of the participants or in the literature.

(Slide.)

Dose optimization, particularly that based upon susceptibility information, a concept was at least touched upon in some of the comments early in the program. It, too, was considered but not included as material for the pre-approval package.

Dose ranges are currently based upon target animal safety, efficacy and residue studies. Due to variables involved in field use situations is not realistic to design adequate studies pre-approval to arrive at an optimal dose, an "optimal dose."

(Slide.)

As we move from the pre-approval arena into the post-approval monitoring program, the pre-approval data should lay the foundation for moving into the post-approval monitoring program for any given drug.

The entire pre-approval package should be supportive and all the information involved should be considered important but any one single study should not result in a pass/fail determination because it was considered to be a prediction for

potential change and susceptibility.

(Slide.)

Finally, and these are mine that the group didn't really get to see, so this is where we could get into trouble.

(Laughter.)

As we look at things, the science of the subject of antimicrobial susceptibility and pathogen load continues to evolve. And for the approval of new products, the process of approval safe and efficacious drugs really cannot wait for the ideal modeling systems to be developed and validated because it was apparent to most of the knowledgeable people in our group that those systems, an ideal model, is currently not available.

Something you can plug in information and come out with an answer is just not available today and we really just can't wait for that. However, the pre-approval studies can and should be integrated with effective post-approval monitoring programs to protect the public health. Thank you. Another one of my functions here is to help Dr. Wages get going.

(Laughter.)

DR. WAGES: And a fine job you've done.

DR. RIDDELL: That's a first.

SUMMARY OF AVIAN BREAKOUT SESSION

By: Dr. Dennis Wages

DR. WAGES: I want to thank -- well, I was going to

be smart when I first got up here and say that when I first gave my earlier presentation the other day, I did not thank CVM for the invitation which was an error on my part, but now I'm not so sure in the last three days I've had anything to think I should thank CVM for this.

(Laughter.)

But no, I do appreciate the opportunity to give some thoughts and I'd like to thank Jeff Gilbert and David Grau for their help in the process for our workshop in poultry.

(Slide.)

When we first looked at the whole question arena in our group, I think it was evident that we needed to look at maybe a model first, and the way we're going to go through this is the thoughts and objectives of the pre-approval data collection, what do we need? How would we go about getting it?

And then, then I'm going to kind of just run through some specific comments that may or may not have been consensus but were involved in coming to some conclusions and I've made three bullet points at the end that I think were overwhelming within the group and I want to thank the group for that.

First thing, before we could identify the -- answer some of these questions on concepts was to define the model first and be able to defend it and adequately critique it as far as its objectives and its attributes in defining and

determining the potential for antimicrobial resistance.

(Slide.)

It was important in the process to know the Framework document categorization, knowing up front where a drug resides in one or two and if we know these categorizations, then we felt that the objectives of the studies should be to basically study the rate and extent of resistance development in target pathogens in poultry as well as when we looked at defining the organisms involved for the development of resistance, it was important in poultry to look at salmonella and campylobacter and commensal organisms however they pertain to the drug/bug interaction, if you will.

There may be instances, and there was evidence brought out that E.coli could be used in the commensal relationships or if you're dealing with certain gram positives enterococci.

There was a concern to put this all in perspective as far as define and actually identify the interpretation of these results and how they would be included in the pre-approval process in a package results of these studies.

(Slide.)

And we felt that if we were designing study -- we felt that the data that we would like to have, when looking -- and I apologize -- I guess I should -- I'm not a good computer person. Gates, would --

(Laughter.)

Because I'll mess it all up here real good. We felt that pre-approval data should include a microbiological package, if you will, of information. And this could be acquired by literature research or literature search. It could be provided by the sponsor.

Many of the drugs that we utilize in poultry, if you look at the reality of things, they're hand-me-downs from humans. They're already established as far as mechanisms of actions and information about the activity itself.

And so that information package may be very easy to be acquired, either through literature searches or the sponsors themselves. And early on in that package, if there is an identification of the risk factors involved, either in animals or humans, those need to be identified.

(Slide.)

Spectrum activity, which was brought up in the ruminant, is an important part of that antibiotic or microbiological package if you will. Resistance -- we need to know and most of the time, when these -- unless we have a new class of antibiotics, the determinants that play a part in resistance are known and those need to be included in that package of information.

And once we identify the resistance determinants, what bacteria have those and is it important to the pathogens

or the commensals that we're dealing with in poultry?

(Slide.)

It was important in the data, much again like ruminants have done, the baseline information -- I think if you look back at the way antibiotics have been cleared in the past, basically we get a clearance and we say, well, you know, we've got this temporal response or resistance that's been acquired after you all started using this in poultry or in food animals.

And then the question becomes, well what was it before we started and the answer is, we don't know. We need to have that information and that needs to be a very proud tool and a consistent tool in pre-approval, and it also allows us the baseline for the post-approval monitoring in identifying change.

(Slide.)

Pre-approval field survey, the NARMS is an excellent tool. It's an excellent process, excellent information. We need to beef it up. I hate to use -- I wish we had a "poultry it up," but that just doesn't sound the same.

(Laughter.)

But we need to increase its usefulness, maybe incorporate the new antibiotics before approval into that system so we have a baseline of prevalence. So NARMS has been a good -- and then, use literature. There's a vast

availability out there that can be tapped into.

And then we need to look at our target organism, what we're trying to treat and survey its pathogen resistance. If that fails in the industry on our end as end users, the potential for zoonotic impact is a moot point because we won't be using it and there won't be any exposure. So that's still an important part and we don't want to lose sight of that.

(Slide.)

Well, and I repeat, well-designed animal studies, and here's where the leather hit the pavement, I think. I think if we look at what we would like to see, and I say we -- this is that group. We had very little to do with information gathered here.

We need well-designed studies that provides data on the impact, the effective dose or the target dose or the end dose, I guess, on the rate and the extent of resistance emergence.

In both the target pathogens, and sometimes we -- I know this is a food-borne deal but we still don't -- shouldn't lose sight that the target pathogen is important as well as our zoonotic and commensals that we've identified.

(Slide.)

We all said that was just greater than sliced bread, but the practicality came in in trying to design those studies and a lot of discussion, and these are some of the challenges

that we found in poultry.

If salmonella is the culprit, the prevalence is low in bird. It's an intermittent shedder. It's not consistent. So do you go in and challenge these birds? Which salmonella do you use? How much? Do you change your model?

Do you change your resistance profile by a challenge model? Which serotype? Which phage -- I mean, you can see, on and on, and read. And is it really a predictive of what's going to happen once this thing gets in the field and we're using it?

Is it actually -- it's intent is to give us a predictive value and I don't think we came to a conclusion that it could do that and we still relied on post-approval to identify such events.

(Slide.)

Question of the value of the data from animal studies -- we really looked at -- there was a lot of information that we are expecting from one and two, meaning the surveillance data, the literature search, what the sponsors -- and the information is out there -- what more do we gain from the animal studies? The value is questionable.

(Slide.)

Challenges in campylobacter, a little easier to find in poultry, but not as easy when you start -- which one do you test and which one are you talking about and do you have to

have a challenge to find it?

(Slide.)

Okay. That was kind of our bullet points and I just want to run through real quickly -- how am I doing, time wise? Just comments that are thrown out and that helped us arrive at those conclusions, and some of them I won't go through much because they're pretty self evident as far as defining the class and resistance, etcetera.

But, identifying the mechanism of resistance and documenting that and confirming that is very important, even at the point of valid in vitro studies on how that resistance occurs was an important -- but also trying to carry it to the field in that situation to be predictive for it.

(Slide.)

That mechanism, whether it be plasmid or chromosomal, do we have information on antibiotics that are out there now that potentially are going to be used in poultry? Do we have information that gives us a comfort zone that, yes, this is a slow resistance developer; no it's not and would give CVM some ability to make some decisions. Of course, in vitro was much more easy to validate than an in vivo change.

(Slide.)

Dosage, this optimized dose. You know, we still are very concerned that dose needs to be effective for what we're trying to treat and everything else is moot if that doesn't

work.

But is there -- you know, and one thing I wanted to put out that we didn't have in our workshop, the AVMA's position statement on judicious antimicrobial use states, "We're going to optimize therapeutic efficacy while minimizing the development of resistance."

So that is an AVMA, a national --- CVM, probably CDC in a global initiative. And maybe it's time to look at marrying those doses and optimize them both if we can, target pathogen resistance versus the resistance in the zoonotic or commensals.

Concern about CVM, how is this data going to be used and does it really have a big effect on the approval process? There will be a lot of information gathered prior to that.

(Slide.)

It was thought that pre-approval surveillance data information would be a very important part of our baseline to monitor post-approval monitoring and serve as our baseline and then observe changes based on that.

(Slide.)

Genetic mechanisms and the way resistance occurs was very -- came up a lot, and I think that adds credence to its importance on how and why things occur and research will probably continue.

Post and pre-approval monitoring via the NARMS, it's going to tell us a lot. The NARMS data is a good tool. It's at tool right now. It needs to be beefed up and utilized, not only the post-approval on what's happened but prior to it and I think now that it's in place, it's a lot easier to put that in the pre-approval program.

Judicious use guidelines are going to play a role in this whole situation and our goal would be to minimize resistance development through the best use. In poultry, one of our first things we say is, the best way to preserve our antibiotics is don't take them off the shelf and use them in the first place and I think that's what we have to look at with our guidelines.

Dosage regimens are important. Again, the optimzing dose was something that came to and from -- came up now and again, trying to marry those two up but not lose sight of what we're trying to treat in the animal.

Pathogen load, that was the easiest part, took fifteen seconds -- not relevant in the pre-approval process; next question.

(Slide.)

Mimic field conditions. We understand that even though as practitioners, the closer we come to that chicken house, the better I feel about things and probably the better a lot of us feel. Those are hard to validate. They're hard to

reproduce and those problems are evident.

(Slide.)

We do believe and confirm that of many things we do in this assessment is for human health impact, and that's -- you know, even though I said we don't want to lose sight of what we're treating in the animal. We're here because of the potential that exists for the human health impact of what we do.

And CVM needs to justify what they do and they said that they're going to do that, based on as much scientific evidence and data that they can collect to justify to whoever, whether it be CDC or congress, that we've approved this drug because of X, Y and Z, and are confident that -- and we have things in place to observe and be able to intervene if we need to.

(Slide.)

We considered the specifics of modeling and most of them we went through, kind of in a general -- because all of them are important in the field conditions, the dose. The route is important. Clearly, an injectable from an exposure standpoint would not be to the point of a feed greater or water soluble in poultry.

Whether we're using a day old chick or a six week old chick or a breeder pullet, replacement makes a big difference and those are all considerations but they're pretty much

relevant in the pre-approval process as the sponsor comes with it.

Withdrawal considerations, once we take that drug away, I think there's an interest in looking at, does that resistance stay on? Is there a persistence? Does it change? Does it go down and does it affect the end potential carcass contamination, etcetera?

A lot of arguments -- not arguments but questions over, when you get into these studies, when do you sample? How do you take it? How much is enough? Is it a gram? Is it a ten grams? You know, what do you do, and the validations are of concern.

(Slide.)

When are some of these studies to be done on pre-approval? There was concern that do you test for the effectiveness on how we're going to use this antibiotic to treat poultry and then hope to heck it doesn't impact as a zoonotic resistance impact.

Or do you do that for saying, and say, this has a lot of cross-resistance. It's a high class antibiotic in the one category; do we stop now and go for companion animal clearance?

Those are concerns and those are valid concerns because if you look at something that's effective but does have the potential to have severe consequences from a zoonotic, I

think those are real questions that a sponsor would say, it's probably not worth going forward.

We talked about the problems with salmonella and campy and there are three kind of bullet ports -- pre-approval data and information is paramount. Getting them by specific animal studies is in question, and the value of that as being predictive.

There's no question that the information is not important. How we get that information and doing it in studies -- I'm paraphrasing and I will say right now, the people in my group and the open comment period, if this is not a good reflection, please stand up and give me what for.

(Slide.)

The pathogen load studies are history in our workshop's view. They're of no relevance or value in the pre-approval and the bang for the buck, if you will -- I can't go down any farther -- is the post-approval monitoring and trying to have a good baseline, what happens before we market that drug and what happens afterwards in the post-approval arena where we can identify changes and have intervention strategies or mitigations based on those values.

I hope, again, I represented the group the way it should have been. Thank you.

(Pause.)

By: Dr. Robert B. Morrison

DR. MORRISON: Thank you. I think you'll notice some common themes which is good. In the swine group, what I'd like to acknowledge, Chuck and Aleta. I think we had a really good group going, and again, hopefully like my two predecessors, I hope I am going to capture the content correctly.

But first off, I think there was one major point that the group wanted to make and that was this one -- by the way, we didn't -- while we weren't trying to seek consensus, sometimes -- a lot of the time we seemed to have it. And so, you'll see some disparate comments in here about particular issues, but for the most part, I would say we had consensus although we weren't trying to seek it.

But the big comment was that the pre-approval studies cannot at this time be used to accurately predict the rata and extent that resistance will occur once the product is approved, a big general, strong feeling there.

But these studies could be used to develop the information required or useful for post-approval surveillance and possibly, in addition to help, identify "red flag" areas that could lead to additional pre-approval studies. So if out of all day long of meetings there was one point that the group wanted to convey, that would be it.

(Slide.)

I'm going to give just some general comments

that were sort of made during the session and then I'm going to talk about what our group thought were the objectives of the pre-approval studies and then we'll address the five questions.

So, in general, just a few comments here and there. We thought that it would be valuable if there's still interest within CVM or others to incorporate pathogen load, we thought there was enough -- that perhaps a different workshop could be held on that because I think, generally speaking, our group wasn't sold on that but there were individuals who thought it might be worth it.

The standard for acceptance of pre-approval should be set a priori and there is a need to develop the decision making process that delineates how these pre-approval studies will be used. We struggled a little bit at the beginning, trying to define the answers to these questions when we weren't sure how they were going to be used.

(Slide.)

Continuing, technology may not be available for determining optimal dosage to maximize therapeutic effectiveness while minimizing the development of resistance. And if post-approval studies are robust, what is the value of the pre-approval studies? And again, these are comments. Perhaps those pre-approval studies can help direct those post-approval studies.

(Slide.)

A question that was raised and perhaps there was no answer for it; we didn't answer it, but should we use a standard and judge new products relative to it. That was if there is a threshold, perhaps there's an indicator agent that we could use. And again, we didn't answer that.

(Slide.)

So then we talked about the objectives of the pre-approval and we were told, as you see here, are these studies pivotal to the drug's approval? Yes, as we were told; and so that then influenced some of the views.

Some members in the group felt that these pre-approval studies should be designed for gathering information only, to compose a body of knowledge that would be then used in the post-approval process. An evaluation of these studies would become part of the risk assessment of the product's approval.

(Slide.)

Again, on the objectives, the major objective of the pre-approval studies could be or would be to characterize the rate and extent of resistance development and studies to address that might include mutation rates of resistance in vitro, the presence of resistant genes to drugs, the frequency of transfer.

In vitro was thought possible; in vivo was

questionable, thought questionable. And lastly, MIC testing for known zoonotic pathogens.

(Slide.)

And finally, with regards to objectives, to determine the level of -- again, that these pre-approval studies, it would be valuable to help direct post-approval surveillance, but the group felt like these studies might be used to modulate or to influence how a compound is ultimately categorized.

While we understand that it comes in and it's categorized in some category, and that might influence the studies that are then done, having completed those studies, perhaps a re-evaluation of the categorization might be appropriate.

(Slide.)

And lastly, these studies would be helpful to better direct the usage of the product.

(Slide.)

To answer the questions, then, what are the positive aspects of the study concepts that had been presented over the previous day and a half, with regards to mathematical modeling, the group felt like those would enable one to test hypothetical scenarios, to assess possible effects of interventions and could fit into larger risk assessments.

In vitro studies, the strengths would be that they could screen a large number of issues and one would have

greater control.

(Slide.)

Limitations, all studies -- this is, I think, an important point that the group felt -- all studies are limited in their predictability of what would actually occur in the field, and you heard that in the previous two groups also.

That the mathematical models, that it was felt that available expertise is limited. They require many assumptions that are open to challenge and there may be difficulty in understanding the outcome.

(Slide.)

Other limitations -- okay; again, there was a feeling that these pre-approval studies can be as robust as necessary to help direct -- well, sorry -- that the pre-approval studies should be as robust as required.

There was a recognition that the existing method, the 558.15 is not adequate. And then we started talking about the agent and host and environmental factors and the limitations.

We felt like in vitro studies, we're limited because of the controlled environment and perhaps the lack of predictability. In vivo studies, the limitations being the limited animal numbers and the high cost, and the limitations on field studies are the difficulty in achieving controls and repeatability.

Another point -- as the level of complexity of the study design increases the reproducibility, decreases, and I think we heard that in several presentations during the day.

(Slide.)

With regards to pathogen load studies, there were three lines of thought. Firstly, that they should be considered. Secondly, that they should not be required for therapeutic products; and thirdly, that they should be eliminated completely. So, we didn't have a consensus there.

(Slide.)

With regards to the second question, we felt like we incorporated that second question in with our first, and so, that question was related to types of data, etcetera, and we felt like we covered that.

(Slide.)

The third question, what factors should be considered when modeling resistance? First off, we said, well let's talk about resistance modeling and some general comments were that the factors that affect the model may change from product to product.

Secondly, a lack of information may or will complicate the study design and the interpretation. Thirdly, that the complexity of design will limit the applicability of transferring this information to the field.

And fourthly, a strength, perhaps, mathematical modeling can identify factors that may substantially affect or influence that post-approval process again.

(Slide.)

We then said, well, all right, we can categorize the factors. The question was, well, what factors should be considered? And having given you, then, those general comments, we said, well, there's generally four lumps -- we're lumpers.

And we said there's four lumps or groups of factors, the first one being the drug factors, the class of drug, the spectrum of activity, the degree of gut exposure, the treatment duration and the withdrawal period, and you might want to include or a modeler might want to include one or more of those in the model.

Secondly, there are agent factors with regards to the target/zoonotic or commensal species, not specifics I believe. And then that would depend upon the species, the strain and the mechanism of resistance.

(Slide.)

Thirdly, environmental field factors, this is, of course, an infinite list that one can define and we just said, well, here's a few -- herd size, disease status of the herd, waste management system, herd management, feed source and that can go on for a long time, that being one of the reasons why

field studies are so important and yet so difficult to reproduce.

And host factors would include but again are not limited to genetics, "stress," age, the age of the herd or the age of the host, the health status, the immune status, etcetera.

(Slide.)

The fourth question, what bacteria should be the focus of pre-approval studies, there was consensus that the target organism, obviously, and then from there on, it was a, well, it depends.

Selection of others depends upon which pre-approval study is being considered, and really, perhaps the question was, well, maybe it's just the target organism. We said, well, you consider a sentinel or indicator bacteria, perhaps E.coli, but when you start saying, okay, well, we're going to include other bacteria in our pre-approval process, you get a bunch of questions that were raised.

For example -- which makes it difficult. If you were going to select campylobacter, would you select campylobacter coli or cambylobacter jejuni? If you were to select a salmonella, which strain and which phage?

And I would just list that a few of the points that were raised were, if you are going to go for other bacteria, then you raise a whole host of secondary questions that makes

this question difficult.

(Slide.)

How should the appropriate bacteria be selected? Two ideas -- one, to consider the spectrum of activity of the antimicrobial. And secondly, consider the importance of that agent or those agents to human health, while regarding swine as the source.

(Slide.)

Thirdly, should surrogate organisms be used? We were first off not sure what a surrogate organism was and so, we tried to answer the question, not really knowing that but if we understood -- if you were going to use other organisms, we thought, well, here are some ideas that surrogate organism might be an indicator organism with a propensity for resistance, sort of as a screening, a worse case screening tool with a preference for a zoonotic species.

A second idea might be an ATCC well-characterized bacterium that a lot is known about. A third might be a bacterium that is ubiquitous or widespread. For example, E.coli or enterococci that are resident, well understood organisms. So, that's all we said about that particular question.

(Slide.)

Are there alternative approaches or concepts that have not been considered? This is sort of a fun question, I

think, because people said, well, what else could we do or what could we do different?

Having gone through all of the discussion so far, we said, well, you know, we've got to remember where these pre-approval studies lie relative to the post-approval process and relative to risk assessment that we thought, you know, we've given a lot of discussion to these pre-approval studies but that it's really important to stand back and say, where does the pre-approval process lie relative to these other two, risk assessments and post-approval?

There was a suggestion that it would be valuable to screen a bank of organisms for resistance to the proposed product to establish a baseline for the post-approval process so you know where you are prior to when you introduce the product.

Thirdly, there was a suggestion that this pre-approval process could be greatly expedited if one was to categorize new antibiotics and their use in humans and prohibit the approval of subtherapeutic use of these antimicrobials in livestock and those that pose a significant "risk" to human health. That if that was simply the decision that that would expedite some of this.

(Slide.)

And lastly, an idea was, when possible to create resistance towards the product in the lab and then study the

mechanism by which the resistance was developed, that might be revealing.

That concludes our comments from the swine group. Thank you.

SUMMARY OF AQUATICS BREAKOUT SESSION

By: Dr. John R. MacMillan

DR. MacMILLAN: Well, I also would like to thank CVM for this wonderful opportunity. It's rare that aquaculture gets invited to these sorts of meetings and I can see why my associates in aquaculture don't try to come to these meetings.

(Laughter.)

But it has been a bit of an eye opener for me and I really am grateful for the opportunity to witness all of this.

(Slide.)

One of the things that in the aquaculture breakout session that we were fortunate to have was very few people attended the breakout session, which really made for a very intimate opportunity for discussion of the issues.

We had a diversity of people there, but we did have very few people and that somewhat compromised our ultimate ability to feel confident that we well represented what could be done in aquaculture.

We had about anywhere from eight to ten people participate and the bulk of those people were from the Food and Drug Administration. We had one representative from a drug

company and which we were really -- well, I'm really thankful for because that means there's some interest there.

But it does hamper our abilities to provide real in-depth comment on some of these issues. The group thought that it would be important to highlight, again, some of the unique features about aquaculture in the United States.

The first thing is that we're a very diverse industry and really we're an industry -- we have a bunch of sectors that comprise the aquaculture industry, the sectors being catfish, trout, salmon, all those things -- all those aquatic animals that we raise, and we raise both food animals and nonfood animals.

And depending on who you're visiting with, the nonfood animals have just as much potential as a food animal -- the nonfoods have just as much potential as the food animals to impact public health.

My feeling, of course, is that we have very, very low opportunity to impact public health, but I can tell you there is not universal agreement about that. We also only have, in aquaculture in the United States, only two approved antibiotics.

In some respects that's an advantage, but in other respects, that's a real disadvantage, not so much from the animal health or animal welfare standpoint. It's certainly a disadvantage from the animal welfare standpoint, but it creates

a problem for us when we try to mitigate the impact of resistance, and I'll get to that in a little bit greater detail in just a moment.

Another feature about aquaculture is that we have many, many different culture environments that we grow the fish or the shellfish, and that makes designing any type of pre-approval studies very, very difficult.

All of the aquatic animals, all the aquaculture to aquatic animals are minor animal species. The consumption patterns in the United States are very difficult to track. It's very difficult to do statistically valid sampling because there's not nearly enough consumption.

Now we could change all that if everybody here would start eating fish once or twice a week. It's really heart healthy and I'll --

(Laughter.)

At any rate, that is a problem for us. Another factor, and this probably applies to all animal industries under consideration today, is that there are multiple inputs of potentially resistant bacteria into the field.

In aquaculture, we have birds flying all around our facilities all the time. We have a lot of aquatic birds -- geese, for example, and herons, that love to eat -- or herons, anyway, love to eat fish and in the process of doing that, they lose some of their waste behind.

Well, those aren't fish wastes; those are warm blooded animal wastes and they can buy us interpretation of what goes on in the field, very dramatically. So a real significant problem for us when we think about trying to design some studies, pre-approval or otherwise, to accurately reflect what goes on under aquaculture conditions.

(Slide.)

I've already mentioned, in our particular group, the scarcity of public input into this process. There are some consequences to aquaculture because of the lack of approved antibiotics.

Because we only -- in aquaculture in the United States, we really only use antibacterial. That's oxytetracycline. The other antibacterial, ROMA 30, which we were really glad to have at the time, has not proved to be as valuable for us as a group as we had hoped.

ROMA 30 has an extended withdrawal time for celmonids. For example, the withdrawal time for celmonids is forty-two days. That's a real disadvantage for us. The withdrawal time for oxytetracycline is twenty-one days.

That's a little bit better than ROMA, but it's still a real -- it's a burden on us and we can appreciate the reasons for that, but what happens is that we have very -- we only use on antibiotic.

And, the consequence of that is that we are

definitely selecting for bacteria that could be resistant to that antibiotic. We don't have any options for drug rotation and one of the comments that has been made the past day or two is that drug rotation can be a valuable tool for minimizing the chances of resistance development.

(Slide.)

Our breakout group felt that, when we started looking at the concepts that we need to look at for pre-approval studies, and I think we're all in very much agreement up here, is that if the candidate drug doesn't have any significant potential for development of resistant human pathogenic bacteria, perhaps pre-approval studies are not appropriate. We think, from a minor animal species perspective that -- well, basically you need to leave us alone.

(Laughter.)

Our potential impact is very, very low in the total scheme of things. Sure, we could impact public health, but in the total scheme of things, our potential is very low. We're just too small, as a group, to do much.

But we thought that any parameters, any pre-approval parameters that are developed, should be relevant. They should be predictive and they should be repeatable. And I think, again, that's what many of the speakers appeared before me have highlighted the real critical importance of those three features.

And as we went through examining various possible pre-approval studies for aquatic animals, we always came back to those three focal issues.

(Slide.)

So, we thought that the first question that was raised in our agenda perhaps wasn't appropriate for us to address very much, so we went on to the second question and that is, what role could the various types of data play in evaluating microbial effects?

(Slide.)

For aquaculture drugs, we thought -- and a lot of this information is gathered already as part of the approval package that has to go forward for an NADA. The chemical, physical properties of the drug were very important to be known.

We thought that it might be valuable, and it definitely is valuable, to note the mechanism of the action of the drug is. These are things that are already required. We thought that it would be important to know the mutation frequency as a consequence of exposure to the drug.

We thought it would be valuable to know the mechanisms of resistance and we thought that it would be important to know the susceptibility profiles. All of these are in vitro tests which we felt could be, if anything could be, those things could be reproducible and verifiable and you

could do it in a statistically valid fashion.

(Slide.)

What factors should be considered when modeling resistance development and pathogen load changes? Well, again, in aquaculture -- and I mentioned a number of these items on the first day that we met -- the species of fish, the water type, whether it's warm or cold water, whether it's salt water or fresh water or whether it's an estrian water or a mix.

Water quality can be a very, very critical factor in determining how the drug behaves in the water column, or in the sediment, what types of bacteria are present, how a pH, for example, can have a dramatic effect.

Calcium concentration, calcium magnesium concentrations, can have a dramatic effect on the longevity or the bioavailability of a drug in water. There have been some studies done in marine environments which indicates that oxylenic acid -- this isn't in the United States but in Europe, for example -- oxylenic acid gets bound up to calcium in the water column under marine conditions and is no longer biologically available.

The point being that water quality can have a dramatic effect in all of its permutations on what happens to a drug in that environment. The type of aquaculture system can also be very critical or crucial for determining potential fate of drugs or resistant organisms in that system.

Closed systems, that's the recirculating aquaculture systems, ponds, net pens and raceways all have similar but also some different factors to consider. And again, we have to be concerned about the different inputs into the system.

In some aquaculture systems, alligators, for example, are very frequent visitors and I know some of my counterparts in aquaculture have always been anxious for a regulatory person to show up --

(Laughter.)

-- when an alligator happened to be visiting. I'm not sure exactly what they had in mind, whether it's just -- well, you can use your imagination, but it is -- these are things that really affect what happens out in the field and makes it very complicated to use field studies to predict what's going to happen.

(Slide.)

What pathogens should be the focus of pre-approval studies? And then the other questions -- how should the appropriate pathogen be selected? And should surrogate organisms be used?

(Slide.)

We, as well as my associates up here, felt that the target animal bacterial pathogen should indeed be a focus of attention. We thought that there was some need to look at human pathogens that might be present in aquaculture production

situations.

It's very difficult to select one in particular, or two in particular -- again, because the water quality conditions, the temperature conditions, all those factors are so variable, or can be so variable.

(Slide.)

But we did -- we felt bold enough to make some suggestions. Listeria monocytogenes is one that could be looked at. Right now, as I understand it, FDA has a zero tolerance for listeria monocytogenes in the processed fish and the consumable product.

So, it's not -- listeria monocytogenes probably would not be a good organism, organisms, to follow in post-approval studies. Vibrio species, there's a number of vibrios that are out there in saltwater environments that would be of interest and could be of human safety consideration, and salmonella certainly is another possibility.

Some of these organisms probably don't reproduce, or if they do, they reproduce very, very slowly under most aquaculture conditions, particularly the colder water aquaculture conditions.

And then we thought there could be some interest, or could be some value, in looking at bacteria that are not of food safety concern, but nevertheless might be in the aquatic environment under aquaculture conditions as well as

nonaquaculture conditions that could potentially be pathogenic to people.

Perhaps some of you have heard of fishmonger's disease. That's a potential organism of people that harvest wild fish with nets, they get abrasions on their fingers and open sores, and certain kinds of bacteria can move into and invade those abrasions and that's a possibility.

(Slide.)

So are there alternative approaches or concepts that have not been considered by FDA?

(Slide.)

Well, we thought there was a need for additional research, but these would not be part of the pre-approval package. We thought that there was a need to try to identify, to give it an effort to identify sentinel bacteria.

These would be bacteria that fairly well characterize, in aquaculture, a typical aquaculture environment. They'd have to be found in many fish species and many types of water.

They have to be easy to grow and characterize, and a lot of this is pie in the sky, in my view, because you're probably not going to find the ideal bacteria. We would also want to look for bacteria that would be representative of what's happening in the real world, and then of course, not currently resistant to any test drugs or current drugs that are

out there.

(Slide.)

We did think that we could, perhaps in the next three to five years, develop a research program; again, not part of the pre-approval program but a research program that would look at -- try to address some of the issues that have been raised during the course of the past two days.

We think it is important to look at bacteria in the terrestrial environment and in the aquatic environment that could be recipients of resistant factors, antibiotic resistant factors so that we ought to develop a national surveillance program, but the program needs to be rational and that may be the most difficult thing to do.

We thought that perhaps we could identify some model organisms that could be used in current studies or prospective studies, but also down the road, retrospective studies with regard to antibiotic resistance. And then, the key issue for us is getting the research dollars to do this, develop these kinds of studies.

(Slide.)

We did identify some pre-market goals. We thought that perhaps some pre-approval studies could be used to optimize dose strategies that we could use to minimize the chances of antibiotic resistance developing and then perhaps help guide us in determining the conditions of use.

Many of these things already go on, but perhaps we could look at some pre-approval studies that aren't currently required to help us out in that regard.

(Slide.)

A lot of our focus was on post-market surveillance, just as with many of the other -- with the terrestrial animal programs, and it's probably not all that important to go through these, except to highlight a few things.

One, that we need to look at target and nontarget bacteria. We need to be able to change the drug use if it's appropriate, and that's going to be difficult to judge what's an appropriate way to modify the drug use.

We think that post-market surveillance might be helpful in helping us adjust management on the farm, and fish farmers have not traditionally thought about ways to do that. Right now, the fish farming community is just interested in survival, getting enough product out there to where they can stay in business.

But perhaps over time, we might be able to design some farm activities that might minimize the chance for resistant bacteria occurring in animals that ultimately ended up in the public domain. And I think that was it. Thank you.

CHAIRPERSON THOMPSON: Okay. I think what we're going to do, it's been suggested to take a short break, about

ten minutes, before we start the open comment period. So, if we could do that now and try to be back here around 2:30.

(Brief recess.)

OPEN COMMENT PERIOD

By: Dr. Grau

DR. GRAU: Okay. We're going to begin the comment period, during which time, if there is anything you'd like to say about what you heard this afternoon or any other perspectives that you'd like to provide, this is your opportunity.

I'll go over the guidelines for providing comments. Please step up to the microphone and give your name and with whom you are associated. Please try to limit your comments to around two or three minutes.

If the panel has points of clarification, any members of the panel, I welcome any or all of you to provide that clarification. And this is a time, this is sort of a time for listening and not debate and that's about all I have. So, if someone would like to start off, please, please go ahead.

DR. GOOTZ: First up, first out. Tom Gootz from Pfizer. I'd just like to comment that I think the past couple of days, we've certainly reached a consensus that thorough development of a pre-approval microbiology package will be critical in establishing an accurate baseline database for all new antimicrobials brought forth.

And certainly, we do have to address all the concerns and issues that human medicine has brought up and other public concerns regarding our continued development of resistance to antimicrobials in animal health, so obviously we have to address that.

And I think, to a large extent, the Framework document, in and of itself, provides some of that feedback in the sense that it does have a category classification, one, two and three categories, which I think, particularly for category one compounds, obviously will raise the bar with respect to sort of the quantity and quality of data that we're going to have to provide for a sound NADA submission.

The scientific consensus again, though, seems to strongly reinforce, from the various people that we've heard over the past couple of days, that it's really the strong data baseline that would be the best groundwork for a meaningful post-approval monitoring studies.

In that sense, I think it is the really total pre-approval package that will be important and that individual studies submitted within that particular package really shouldn't stand alone as typical or, by that I mean pass/fail studies, but it really is the strength of the total package that hopefully CVM and the sponsor will work from and consider very carefully.

Certainly, CVM and other government agencies such as

the CDC and USDA and the sponsors themselves I think should continue to communicate in a much better way, more constructive way, on how to design surveillance programs, especially with taking advantage of some of the newer technology that's out there such as pulse field --- sequencing of specific resistance genes and trying to study the linkage of specific resistance genes in the environment.

But I think our ability to do that is best conducted in a framework where we evaluate both the technology but also the practical use of it and we have a real understanding from a lot of people in this room of how that technology can apply to assessing resistance in terms of how the drugs are used in the field.

And lastly, I would just say that we and the CVM, CDC and the sponsors communicate and weigh the value of sound pre and post-approval data and try to address some of the pressures that are being put on our industry and our practices.

And I think really only in that way, if we really try to sort of work together and make sure we don't spring some surprises on one another or with a baseball scenario, try to steal home plate and get caught between third and home, we'd really be able to, in a legitimate and satisfying way, try to address and hopefully someday answer the risks that are associated, both from the human health area, other government agencies, as well as the concerns that are being raised within

the industry itself regarding the risks involved with discovery and development of new animal health antimicrobial agents.

DR. GRAU: Thank you.

MR. SCHUSTER: Dale Schuster, Schering-Plough. I just want to leave with a thought that doesn't leave a misconception -- that is, we are in favor of doing pre-approval studies because they would be meaningless.

We also see that they are unnecessary in that surveillance program that is in NARMS, we feel is fully adequate and, in fact, very adequate to safeguard public health, and in fact, it's the best way to safeguard public health, which means that pre-approval studies really aren't that necessary anyway.

DR. GRAU: Thank you.

DR. SHRYOCK: Tom Shryock, Elanco. In terms of the scope of pre-approval studies, I think in the four breakout groups that we've had, we've kind of been operating under the assumption that these will be for new full submission packages as they move forward.

But we also have to keep in mind that in some cases, sponsors have already put forward into the review pipeline things such as adding another pathogen to an existing label and that, to my understanding, has been allowed the NADA to be opened up to the extent that some of these types of pre-approval studies could be required in a very general and

deep situation.

So, it might be important to consider how much of an in-depth study will be required, given what we've heard today and some of the recommendations brought forth as to whether some of these kinds of things, when you're adding another bug or two to a labeled indication, is that really necessary to go the depth of these types of studies to account for resistance and that sort of thing in a pre-approval type mode. Thanks.

DR. SUNDBERG: Paul Sundberg with the National Port Producers Council, and on behalf of the port producers, what our interest is our interest for our members is timely economic availability of effective products, and we do that for animal health. We do that for animal welfare. We do that for the environment as well as, very importantly, we do that for food safety.

In summarizing the meeting and looking at next steps from our point of view, would be, first of all, that issues such as pathogen load, which using that as a regulatory tool may be difficult if not impossible.

Pre-approval information we used in our swine group, the concept of vectoring, that the pre-approval type of studies that could be done would help vector and push toward an effective post-approval surveillance system, and we think that's extremely important, the post-approval surveillance system that everybody can have confidence in and that can

actually protect public health.

Going back to our comments on the Framework, the original comments on the Framework, it would seem that the Framework, as a total, is more of a research agenda than it is a way to approve products in a timely manner and I think that this meeting helped to underscore that in that there are very many more questions that really point to different areas of research that are multiple, doctoral dissertations than what they are answers, than what we have answers and how we can go.

And in that light, perhaps the agency could focus more on what they can do rather than the research to get some things done that may not be doable, and as far as that doable section, perhaps a focus more on supporting post-approval surveillance, supporting the NARMS system, making that robust enough so that we have confidence in it, the consumers can have confidence in it and we can use that effectively.

DR. GRAU: Okay; thanks a lot. Any other comments?

DR. MUDD: Tony Mudd from COMISA, the global animal health association. I'd just like to make one or two comments which I think may be relevant in the context of how we have been dealing with some of these topics and subject areas as far as the EU is concerned, because one of the specific things which are happening there are present, I think, needs to have our fairly close attention to make sure that there is no

repetition of what's going on.

I think we need to look very carefully at what the appropriate scientific studies are versus the kind of political interference, if you like, which is going on in the context of resistance at the EU level.

At the beginning of this meeting, someone asked the question, how many people that were here who knew something of the pre-antibiotic era? There was not a stampede of people putting their hands up and saying that they knew something of this.

Well I personally, going back to 1945 remember very well that my sister, we almost lost her because of pneumonia. Fortunately, we had a compound, M&B693 which was a sulfonamide at the time, which managed to pull her through.

Soon after, in 1950, I moved to a farm environment and the three guys that we saw most frequently on the farm in 1950, first of all, the feed sales guy; secondly the veterinarian; and thirdly, the knackerman (ph.), the guy who came to take away the dead carcasses and the ones that were so sick we couldn't do anything with.

Subsequently, the veterinarian, a few years later, came along with miracle compounds, little tubes of stuff like this, like the toothpaste on the airlines, pushed these into the udder of the dairy cow and miracle upon miracle, she didn't have to go off to the knackerman.

He also came along with a big metal syringe, metal and glass syringe, and pumped the animals full of a golden substance, and this again was a wonderful transition. If we jump forward, getting on for fifty years or so, we find that the EU process, which is looking at this resistance area, etcetera, suddenly starts implementing precautionary principles, and these are fine, providing proper risk assessment is done.

But unfortunately, what we've seen through history, examples -- for example, coming along initially with scientific approval and scientific justification for, for example, anabolic implants, these were banned. BSD got a scientific approval; that also has been banned.

Now we have a portfolio of antibiotics there in Europe. Once again, scientific opinion said that these were no risk as far as their continued use; these also have been banned. And of course, this is all of very great concern.

Obviously, now that those products have been banned, there has been reversion back now to the use of therapeutic agents. So whereas the poultry guys wanted to use growth promoters, not as growth promoters as they said, but for control of things like necrotic enteritis, colangio hepatitis, which are now very serious problems in the European poultry industry.

What is it they're doing? They're using broad

spectrum amoxicillin therapy. Is that really what want? Now this is certainly what happens when we have a very narrow portfolio of products.

Denmark, of course, has now removed growth promoters from all its big production as of the beginning of this year. Already they are running into problems. Basically, we obviously need, desperately, more antibiotics in this area and let's try and do everything possible to achieve that objective.

In Denmark, in 1998, we had a conference there, looking at the same topic, generally, antibiotic resistance. A senior consultant, medical microbiologist there, got up towards the end of the meeting and said, "I don't really know why we need to spend all this time discussing these topics, these subjects.

It's quite clear that this resistance problem is associated with the way that we in the medical microbiology sector and the way that we in medicine have totally screwed up.

We have been using these products willy-nilly across the board. We've been using, dishing them out like candy, and now we're seeing the problems and the results associated with that."

Animal usage in terms of resistance, he said, is obviously a very, very tiny and minor component of what is

going on here. I think we really need to bear that very much in mind.

Basically what I'm requesting is that -- I don't want to see a reversion back to the early 1950s. I certainly don't want to see that knackerman coming onto our farms again with the frequency that he did at that time.

COMISA specifically, of course, just over a year ago, came out with prudent use, a judicious use guidelines, and obviously, we are delighted to see that various other initiatives have followed that over the last twelve months.

We very much support this objective, but really, let us ensure that whatever guidelines we come up with, whether it's pre or post-approval, are scientifically based and we don't chase down the EU precautionary principle routes. Thank you.

DR. GRAU: Thank you. Anyone else who would like to make a comment? I feel like I have this virtual gavel that's starting to --

(Laughter.)

Okay. All right. Thank you very much. I'm going to turn it over to Sharon Thompson, Dr. Thompson, and thank our panelists for staying up here.

NEXT STEPS/CLOSING COMMENTS

By: Dr. Sharon Thompson

CHAIRPERSON THOMPSON: I have the task of trying to close up this meeting and first off, I wanted to just start by highlighting some of the next steps that I envision with respect to this issue.

And I will say that much of what I'm going to say is maybe not as definitive as people would like it to be, but that's just where we are right now in this process.

(Slide.)

Okay. With respect to pre-approval studies, which is the focus of this particular meeting, I want to emphasize that we do have an open docket where if after this meeting you come up with additional comments that you would like to submit to us, we would be happy to have those.

We would also like to get comments in terms of overall public process, how you think this particular meeting was handled. If you have any suggestions in terms of how we should proceed and gather additional public input, we would also welcome that.

(Slide.)

We plan to review the transcript and the comments submitted to the docket, and based on that, I think our first assessment will be to say whether or not we feel we need more input before moving forward and preparing a draft guidance document.

I think I certainly was not able to be personally in

all of the different sessions, but at least the sessions that I was in, I heard loud and clear that there were questions with respect to what are really the objectives we're seeking to meet with these pre-approval studies. I think that's an important point.

I think we need to really look at that. There was question about some of the studies, specifically pathogen load. Are these really something that we should move forward with? So I think we need to -- CVM needs to consider that and formulate how it's going to move forward on this issue.

(Slide.)

I can say that, in terms of a -- once we decide on our next steps, we did hear the message loud and clear, that we need to clearly define the objectives of whatever pre-approval studies we would require and I think that's an important point.

If we do move forward and develop a draft guidance document, we would obviously, as with all guidance documents, solicit comments on that. I do see that potentially, depending on, overall the comments that we get, we may need to also consider having an additional scientific meeting.

One of the groups, I know, made a comment with respect to pathogen load; maybe we should have more discussion, potentially with respect to even just the subject of this

particular meeting, we need more scientific input on it before we move forward, so we do acknowledge that.

I would also like to point out that we had a heavy contingent from our research program at CVM and we are very interested in trying to look and focus our research on answering some of the methodology questions that were raised during this meeting, so we do acknowledge that that's a priority for CVM and will be focusing on that.

(Slide.)

It was briefly mentioned that there is a working group held under VICH which is the Veterinary International Cooperation on Harmonization. Dr. Bill Flynn is the CVM representative to that group and we were fortunate at this meeting to also have the chair, Dr. Mevius here, to participate in the meeting.

And this group will be meeting in the first part of this year, so I think that that's something in terms of international considerations we can't ignore in terms of the role that group will potentially play on our next steps.

But very much the focus of that group is the focus of this particular meeting, looking at how you address the issue of microbial safety in a pre-approval fashion, whether or not you can predict what's going to happen, post-approval. So we will be participating in that meeting, and obviously, that is also a high priority for us.

(Slide.)

The concept of categorization, I do want to point out that we stated in our response to comments on the Framework document that we are not -- we have not made the decision in terms of being wedded to the specific three categories as proposed in the Framework document.

So as a first step, I think our current focus is on really evaluating that and seeing whether we feel that suits CVM needs and this is really based on some of the comments that were made to the docket as well as during the V-Mack meeting that was held on the Framework document.

So, that's really the first step for us and we're in the process of considering that currently. However we move forward with that, we do, obviously, intend to seek public input and based on the particular mechanism that we choose will really dictate the time frame.

We have looked at putting out just a guidance document. I think we could certainly do that in shorter order than for instance going with a advisory committee which is, I think the other alternative we're considering.

But we will certainly, in terms of keeping people informed, we will put additional information up on our home page as that's available in terms of our next steps.

(Slide.)

I think on thresholds, I can say, I think this was --

the point was made, certainly by Bill Flynn in his remarks, that we are committed to thresholds as a component of the regulatory framework.

We do view this as an important post-approval tool for certain classes of products, not necessarily for all products. We are in the process right now of trying to --- what mechanism we will use to seek public input, whether that will be a scientific workshop, much along the lines of this particular meeting or an advisory committee.

And the time frame I put up there really is contingent on which mechanism we choose. We hope to make that decision very shortly and in the near -- but six months is what we would shoot for with respect to holding another workshop on this particular issue, while if we go with an advisory committee, planning-wise, will take us a little bit longer.

So, I can say that we are committed to moving forward with thresholds, but I can't tell you in terms of specific next steps in terms of when we will have a meeting.

(Slide.)

Risk assessment, as you all are, I'm sure, aware, we did release a draft risk assessment on the human health impact of fluoroquinolone resistant campylobacter associated with the consumption of chicken.

And the comment period for that risk assessment closes actually today. Our plans are to review all the

comments that have been submitted to the docket and to finalize that risk assessment in the early summer.

And we plan to respond to the comments that were received, both at the December meeting as well as the comments to the docket in our final risk assessment so that everyone will be able to see how we have addressed the particular comments received.

(Slide.)

We have also contracted for a second quantitative risk assessment to look at the issue of indirect transfer of resistance from animals to humans and we will be modeling the impact of Virginiamycin resistance in E.faecium in animals on the ability to treat E.faecium in humans.

We have currently initiated what we're calling a feasibility study. As part of that process, we plan to request public input on the appropriate design of a risk assessment model and we will also be asking for the submission of data that will be helpful in supporting the risk assessment.

And I would look for that particular -- what we plan to do is put out a Federal Register notice and I would look for that within the next month, so we are moving forward on that.

(Slide.)

I was very glad, actually, in the comments made on the international perspective from COMISA because it was a

very good read into a point that I wanted to make. I have been very extensively involved in a lot of the international activities on this issue and I am concerned with the need for the U.S. to really develop a strong science based approach to this issue.

And I wanted to highlight some of the activities that are upcoming so that people really understand the urgency in this and understand some of the difficulties that we are confronting.

The World Health Organization held a meeting in January, the purpose of which was to develop draft principles on the containment of animal microbial resistance.

Originally this particular meeting was supposed to focus on prudent use recommendations, but the scope of what WHO has taken on is very broad, including pre-approval studies, post-approval monitoring, controls on veterinarians in terms of how available they will have drugs, how they can sell the drugs.

It's very broad reaching and it's very specifically in this document, the question of microbial safety is addressed and there was basically agreement that some work needs to be done on this pre-approval.

So I think there was a consensus of all the people at that particular meeting that it needs to be addressed. There will be follow up meeting in June with

a larger group of stakeholders to try to finalize these draft recommendations.

But, once again, the U.S. is only one component of this and there are different views around the world, and it's very important that we get your input and really put forth the best science based approach to this issue.

The OIE, the Office of International Epizootics, if people don't recognize that acronym, is also getting into the fray on the issue. They have formed an ad hoc group on antimicrobial resistance which is looking at broad range of issues, monitoring laboratory methods.

I put up here specifically risk analysis because what they hoped to do is to try to define how you should address the assessment of risk with products, really from a pre-approval fashion.

So once again, very much what should you do, pre-approval, with respect to antimicrobial products? And the first meeting is actually coming up in two weeks. So, once again, it's very important that the U.S. has a good science based approach.

Codex is also looking at this issue. The veterinary drug residue committee will be addressing it in March. It's not clear yet what that committee will do with it, so I've put a question mark there.

The Codex committee on food hygiene is committed to

look at this and to try to develop what they're calling a risk profile. Denmark is leading this effort and will be holding a meeting in June to try to draft such a risk profile.

So once again, very much linked to what the work OIE is doing. And I think, once again, just from my perspective and emphasis on the fact that with all the questions that people have, it's really important that the U.S. focus on, you know, what is the best science, how are we going to address this issue to help answer some of these questions.

(Slide.)

So, in closing, I just want to say that we really do need your input and we value your input in terms of developing sound, scientific based policies. We acknowledge this is a very complex scientific and policy issue; there is no question on that.

We understand the need to move forward quickly, but on the other hand, it is a complex issue, so we feel it's important that we deal with all the complexities but we are committed to move forward.

One thing that we are trying to do and we certainly, once again, welcome your comments if you have suggestions for how we can do this better, but we are very interested in public input in all phases of this process, so we are committed to that.

In closing, I just really want to personally thank

everyone who participated in the meeting, all our speakers and especially the moderators who really did an excellent job and I want to make sure that we at least give a round of applause because I really do think their efforts were tremendous.

(Applause.)

So I'd be happy to answer a couple of questions, although I may not have the answers that you'd like, but if you do have some specific questions with respect to next steps. Everybody may just want to leave and get out to the beautiful day that's occurring outside, so thank you.

(Whereupon, the meeting was concluded.)